Mortality and Morbidity of the Small for Gestational Age (SGA) Very Low Birth Weight (VLBW) Malaysian Infant

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ABSTRACT

Objective: To compare the neonatal course of small for gestational age (SGA) and appropriate for gestational age (AGA) preterm infants 1500 g or less birthweight.

Method: A total of 116 infants SGA infants 32 weeks or less were matched with 116 AGA infants of the same gestation, ethnic group, sex and where possible inborn or outborn status.

Results: Significantly more SGA infants had a 1-minute Apgar scores of 3 or less, odds ratio (OR) 2.54 (95% Confidence Interval (CI) 1.25, 5.20) and a Critical Risk Index in Babies (CRIB) score > 5, OR 2.09 (95% CI 1.07, 4.09). They were significantly more likely to have hypotension, 35.5 versus 22.3%, OR 1.90 (95% CI 1.01, 3.59). There was no difference in the frequency of respiratory distress syndrome, mechanical ventilation, infection or rate of congenital malformation.

Mortality before hospital discharge was significantly greater for the SGA infant (52.6 versus 28.4%, OR 2.79 (95% CI 1.56, 5.02)). This difference remained significant after exclusion of congenital abnormalities. Survivors had a longer mean duration of stay, (54.4 versus 41.2 days, p < 0.001).

Conclusion: The higher mortality seen in SGA infants appears to be due to a poorer condition at birth. There is no evidence that SGA infants have more mature lungs so antenatal corticosteroids should not be withheld on these grounds.

Keywords: small for gestational age, preterm, very low birth weight, Malaysia, mortality, morbidity

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The small for gestational age infant (SGA) has traditionally been viewed as tougher and more mature than an appropriate for gestational age (AGA) infant[1]. This notion has probably arisen from earlier studies comparing SGA and AGA infants of the same birth weight[2]. Very low birth weight (VLBW) infants 1500 g or less are mostly preterm but may be either SGA or AGA. In such a population, at any given weight, SGA infants would have a more advanced gestation and thus be expected to be more mature and have a better outcome. The notion that they had more mature lungs and were less likely to develop respiratory distress syndrome (RDS) may have in part arisen from studies where increased levels of stress hormones were found in SGA infants and from the finding that corticosteroids increase lung maturation[3,4]. Tyson et al used multivariate analyses to look at the risk of RDS, respiratory failure or death in infants of the same gestational age born between 1977 and 1980. They found that SGA infants had a higher mortality and were at increased risk of RDS compared to AGA infants of the same gestational age. They concluded that this should be further examined in other and more contemporary populations[5]. Our present study aims to address this question. Using data from the 1996 Malaysian Paediatric Association (MPA) VLBW study, we compare the outcome and prevalence of RDS in SGA and AGA preterm VLBW infants[6].

METHOD

The study was conducted in 20 Malaysian centres caring for VLBW infants. The centres were as follows: 14 in the Ministry of Health (eight general and six district hospitals), two universities, and four private hospitals. The two nurseries in the Hospital Kuala Lumpur complex were considered as separate centres. Centres were identified by a randomly assigned code number known only to the individual centre and the data centre. Inpatient data on all VLBW infants admitted to the participating centers were collected prospectively over a 6-month period during 1996. The total number of VLBW infants was 962 of whom 667 (69%) survived to discharge.

Gestation was assessed using the date of the last menstrual period. When the mother was unsure of her dates the Ballard neonatal assessment was done[7]. Limitations in the number of ultrasound machines available meant that ultrasound dating during the

first trimester was not widely practised in Malaysia during the study period. SGA was defined as any infant falling below the l0th percentile for gestation on the New South Wales growth curves[8]. Because the study group was derived from a birth weight selected population of infants 1500 g or less, all infants above 32 weeks were SGA, and there were no AGA infants to serve as controls. Therefore only SGA infants 32 weeks and below could be studied. Each SGA infant 32 weeks and below was matched with the next AGA infant on the database of the same gestation, ethnic group, and sex. Wherever possible they were also matched according to whether they were inborn or outborn. Severity of illness on admission was measured using the CRIB score[9]. Cause of death was classified according to the Hey modification of the Wigglesworth criteria[10].

Data analysis was carried out using the epi-info statistical package. The chi-square statistic was used and expressed as odds ratios (OR) with 95% confidence intervals (CI). A p value of <0.05 was accepted as significant.

RESULTS

A total of 116 SGA VLBW infants were selected and these were matched with 116 AGA controls. The characteristics of these infants are shown in Table I. There were no differences between the two groups except for the finding of prolonged rupture of membranes in significantly more of the AGA group. This finding only just reached a significance level and there is no plausible explanation for it, it was considered to be a chance finding and the comparison of the two groups was thus valid. A summary of the main findings is shown in Table II. There was a significantly higher proportion of SGA compared with AGA infants with an Apgar score at one minute of three or less, (31.7% and 15.4% respectively, OR 2.54 (95% CI 1.25, 5.20)). There was no significant difference at five minutes. Similarly the median CRIB score was higher in the SGA group (5 versus 3, p <0.01) and significantly more SGA infants had a CRIB score of greater than 5 (47.6% versus 30.3% respectively, OR 2.09 (95% CI 1.07, 4.09)). There was no difference in the proportion of births attended by a paediatric doctor and the proportion intubated in the labour room.

There was no difference in the rate of hypothermia (axillary temperature <36.5 degrees centigrade) or hypoglycaemia (< 2.2 mmol/1). Hypoglycaemia was seen in 34.2% and 27.1% of SGA and AGA infants respectively. Significantly more SGA infants had hypotension, (35.5% compared with 22.3%, OR 1.90 (95% CI 1.01, 3.59)). RDS (diagnosed on clinical criteria according to the usual practice of the reporting Paediatrician) was seen with equal frequency in the SGA group and AGA group, and similar numbers were ventilated for RDS. Infection occurred in 25% of infants in both groups. There were no differences with respect to the proportion of early as opposed to late onset infection or Gram-negative as opposed to Gram-positive infection. There was no difference in the rate of necrotising enterocolitis (NEC), ultrasound diagnosis of intraventricular haemorrhage, retinopathy of prematurity, or oxygen dependency at 28 days.

There was a significantly higher mortality rate in the SGA group, (52.5% compared with 28.4% for AGA infants, OR 2.79 (95% CI 1.56, 5.02)). This significance was maintained when congenital malformations were excluded, (49.1 versus 27.4%, OR 2.55(95% CI 1.40, 4.64)). SGA infants who survived to discharge had a longer mean duration of stay of 54 days compared with 41 days, (p < 0.001). The cause of death is shown in Table III. Due to the small numbers it was difficult to compare the two groups; however, although there was no statistical difference between the groups, there was an excess of SGA infants with a cause of death due to infection.

Table I. Characteristics of 116 small for gestational age (SGA) infants compared with 116 appropriate for gestational age (AGA) very low birth weight infants.

	SGA n=116	AGA n=116	Significance
Mean birth weight (g) (SD)	940 (209)	1229 (212)	P<0.001
Mean gestation (wks) (SD)	30.1 (1.7)	30.1 (1.7)	
Median gestation (wks)(range)	31 (24-32)	31 (24-32)	
Ethnic distribution			
Malay (no.)	71	71	
Chinese	19	19	
Indian	19	19	
Indigenous	4	4	
Others	3	3	
Percent Male sex	52	50	ns
Singleton (%)	94 (81)	98 (84)	ns
Twin	19	14	
Triplet	3	4	
Percent Inborn	82	85	ns
Congenital Malformation (no.)	8	3	ns
Caesarean delivery	47 (41)	38 (33)	ns
Percent with Maternal Factors			
Hypertension	35	24	ns
Premature rupture of membranes	24	28	ns
Prolonged rupture of membranes	9	20	OR 0.40 (0.16,1.00)
Antenatal Steroids (1 or more doses) (%)	29 (26)	26 (23)	ns

Table II. Comparison of morbidities and mortality of 116 small for gestational age (SGA) and 116 apropriate for gestational age (AGA) infants.

	SGA (%)	AGA (%)	Significance*
1-minute Apgar < 3	33 (31.7)	17 (15.4)	2.54 (1.25, 5.20)
5-minute Apgar	22 (23.1)	15 (15.3)	ns
Critical Risk Index in Babies (CRIB) Score			
Median	5	3	p < 0.01
Number with CRIB score > 5	40 (34.4)	27 (23.2)	2.09 (1.07, 4.09)
Hypoglycaemia	29 (27.1)	38 (34.2)	ns
Hypothermia	46 (40.3)	42 (37.1)	ns
Hypotension	41 (35.3)	25 (22.3)	1.90 (1.01, 3.59)
Respiratory Distress Syndrome	83 (71.5)	85 (73.9)	ns
Intermittent Positive Pressure Ventilation	55 (46.6)	54 (47.8)	
Airleak in ventilated infant	10 (18.2)	4 (7.4)	
Total Infection	27 (23.2)	31 (26.7)	ns
Early onset (no.)	7	8	
Late onset gram positive	5	7	
Late onset gram negative	15	18	
NEC	5 (4.3)	4 (3.4)	ns
IVH	19	18	ns
ROP Grade 3 or >	4	4	ns
Mortality	(52%)	(28.4%)	2.79 (1.56, 5.02)
Mean duration of Stay in survivors (days)	54.4	41.2	P < 0.001

IVH - Intraventricular haemorrhage. Only 41 infants in each group had ultrasound examination,
NEC - Necrotising enterocolitis. Bells grade 2 or more ie definite NEC,
ROP - Retinopathy of prematurity. Only 36 SGA and 35 AGA infants were screened,

* Odds ratio and 95% confidence interval for categorical data and p value for means, ns = not significant

Table III. Cause of death for small for gestational age (SGA) and appropriate for gestational age (AGA) very low birth weight infants.

	SGA	AGA
Congenital malformation	5	2
Intrapartum asphyxia	3	0
Pulmonary immaturity	8	3
RDS	21	21
Intraventricular haemorrhage	1	0
Infection	23	7
Other	0	0
Total	61	33

DISCUSSION

In our population of 962 VLBW infants of birth weight 1500 g or less, the mean gestation of SGA infants was 33.5 compared with 28.6 weeks for the AGA infant. In this weight selected population of SGA infants the survival was significantly better than AGA infants. However, by matching the SGA infants in the population with an appropriately grown infant of the same gestation, race and sex we were able to show that small for gestational age infants had a higher mortality. This may be due to an increased severity of illness at birth, evident as a lower 1-minute Apgar score, higher CRIB score and higher frequency of hypotension. We also found that SGA were at least as likely as AGA infants to develop RDS or require mechanical ventilation. There was no evidence for the SGA infants being "tougher" or having more mature lungs. The assumption that SGA infants had more mature lungs is sometimes given as the reason for withholding antenatal corticosteroids from this group of infants. Our findings suggest this practice is unfounded. Corticosteroids were given to 27% of our study population indicating that there is a need to improve the rate of steroid use.

Accurate means of detection of intrauterine growth retardation are needed so that such infants can be referred for delivery and subsequent care in a high risk centre. This would necessitate early and accurate dating of the pregnancy followed by growth monitoring. Delivery of these infants should be attended by trained personnel who are aware of the risks these infants face and who are experienced in resuscitation. The concept of increased risk in these infants needs to be more widely understood.

Several other studies have found an increased mortality in SGA compared with AGA infants of the same gestation[11-15]. They have also found an increase in NEC, RDS, and infection[6,15,16]. We had only small numbers with NEC and did not find this difference for RDS or infection. However, we did find that there was no decrease in these conditions compared with AGA infants. There is variation in the incidence of RDS with race, and it may be those races with increased growth restriction that are also less prone to RDS[17]. It is therefore important to control for race. However, in Malaysia there are three main races, Malay, Chinese and Indian and we do not know whether there are differences in the incidence of RDS in these three races. Because we controlled for race we were unable to address this question.

Populations of SGA infants comprise the intrauterine growth restricted infant and the constitutionally small but normal infant. The outcomes described here and by others would be specific to the growth restricted infant, while outcomes for the normal but small infant would not be expected to be different from an AGA infant. Differences found between studies might depend on differences in the proportion of growth restricted and small but normal SGA infants

in the study group. This in turn would depend on the type of population from which the study group was derived, high risk at one extreme and community based at the other, and the selected growth chart.

Hypoglycaemia is a well known risk for the SGA infant[18]. We did not find any difference in the rate of hypoglycaemia or hypothermia for SGA compared with AGA infants. A recent study shows that early feeding or intravenous glucose infusion can prevent hypoglycaemia although biochemical differences in the metabolism of glucose remain[19]. Our findings could indicate that these conditions are being well managed in our population.

We found a low 1-minute apgar, high CRIB score, and high frequency of hypotension. These findings suggest that these infants were in a poorer condition at birth. Low apgar scores have been reported previously[20], and this has been attributed to the result of a chronically hypoxic infant being exposed to the acute stress of labour[21]. If hypotension is due to asphyxia at birth then the principal pathophysiology is myocardial dysfunction. It should be managed with inotropic support rather than volume expansion. The use of non-invasive blood pressure monitors is not recommended for monitoring these infants as inaccuracies have been reported when this method is used in tiny infants[22,23]. The use of intra-arterial catheters connected to a pressure transducer is recommended.

CONCLUSION

In conclusion, the Malaysian small for gestational age infant has an increased risk of mortality and this may be attributed to a poorer condition at birth. Being SGA does not protect an infant from RDS.

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REFERENCES

1. Wallis SM, Harvey D. Fetal growth, intrauterine growth retardation and small for dates babies. In: Roberton NRC, editor. Textbook of Neonatology. 1st ed. Edinburgh: Churchill Livingston 1986; 119-28.
2. Horbar JD, Onstad L, Wright E. Predicting mortality risk for infants weighing 501 to 1500 g at birth: a National Institutes of Health and Neonatal Research Network report. Crit Care Med 1993; 21:12-8.
3. Yoon JJ, Kohl S, Harper RG. The relationship between maternal hypertensive disease of pregnancy and the incidence of idiopathic respiratory distress syndrome. Pediatrics 1980; 65:735-9.
4. Liggins GC, Howie RN. A controlled trial of antepartum glucocorticoid treatment for prevention of respiratory distress syndrome in premature infants. Pediatrics 1972; 50:515-25.
5. Tyson JE, Kennedy K, Broyles S, Rosenfield CR. The small for gestational age infant: accelerated or delayed pulmonary maturation? Increased or decreased survival? Pediatrics 1995; 95:534-8.
6. The Malaysian Very Low Birth Weight Study Group. Malaysian Paediatric Association Very Low Birth Weight Study 1996. Malaysian Paediatric Association 1998.
7. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr 1991; 119:417-23.
8. Beeby PJ, Bhuta T, Taylor LK. NSW population-based birth-weight percentile charts. J Pediatr child Health 1996; 32:512-8.
9. Tarnow-Mordi W, Ogston S, Wilkinson AR, Reid E, Gregory J, Saeed M, et al. Predicting death from initial disease severity in very low birthweight infants: a method for comparing the performance of neonatal units. BMJ 1990; 300:1611-4.
10. Hey EN, Lloyd DJ, Wigglesworth JS. Classifying perinatal death: fetal and neonatal factors. Brit J Obs & Gynaecol 1986; 93:1213-23.
11. Phelps DL, Brown DR, Tung B, Cassady G, McClead RE, Purohit DM, et al. 28-day survival rates of 6676 neonates with birth weights of 1250 g or less. Pediatrics 1991; 87:7-17.
12. Scissone AC, Gorman R, Callan NA. Fetus-Placenta-Newborn: Adjustment of birth weight standards for maternal and infant characteristics improves the prediction of outcome in the small-for-gestational-age infant. Am J Obstet Gynecol 1996; 175:544-7
13. Piper JM, Xenakis EM, McFarland M, Elliot BD, Berkus MD, Langer O. Do growth-retarded infants have different rates of perinatal morbidity and mortality than appropriately grown premature infants? Obstets and Gynecol 1996; 87:169-74.
14. Ruys-Dudok van Heel I, de Leeuw R. Clinical outcome of small for gestational age preterm infants. J Perinatal Medicine 1989; 17:77-83.
15. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A. Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. Am J Obstetrics & Gynecology 2000; 182:198-206.
16. Beeby PJ, Jeffery H. Risk factors for necrotising enterocolitis: the influence of gestational age. Arch Dis Child 1992; 67:432-5.
17. Kavvadia V, Greenough A Dimitriou G, Hooper R. Influence of ethnic origin on respiratory distress syndrome in very premature infants. Arch Dis Child Fetal Neonatal Ed 1998; 78:F25-8.
18. Lubchenco LO, Bard H. Incidence of hypoglycemia in newborn infants classified by birth weight and gestational age. Pediatrics 1971; 47:831-8.
19. Hawdon JM, Ward Platt MP. Metabolic adaptation in small for gestational age infants. Arch Dis Child. 1993; 68:262-8.
20. Wennergren M, Wennergren G, Vilbergsson G. Obstetric characteristics and neonatal performance in a four-year small for gestational age population. Obstet and Gynecol 1988; 72:615-20.
21. Anderson MS, Hay WW Jr. Intrauterine growth retardation and the small-for gestational-age infant. In: Avery GB, Fletcher MA, MacDonald MG, editors. Neonatology: Pathophysiology and management of the newborn. 5th ed. Philadelphia: Lippincott Williams and Wilkins. 1999; 411-44.
22. Chia F, Ang AT, Wong TW, Tan KW, Fung KP, Lee J, Khin K. Reliability of the Dinamap non-invasive monitor in the measurement of blood pressure in ill Asian newborns. Clin Pediatr 1990; 29:262-7.
23. Lee J, Rajadurai VS, Tan KW. Blood pressure standards for very low birthweight infants during the first day of life. Arch Dis Child 1999; 81:F168-70.

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